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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/598,736	07/19/2007	Sophie Lotersztajn	26600	9624

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EXAMINER	
HUGHES, ALICIA R	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
11/29/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/598,736	LOTERSZTAJN ET AL.	
	Examiner	Art Unit	
	ALICIA R. HUGHES	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20 and 28-37* is/are pending in the application.

4a) Of the above claim(s) *20,30 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,29 and 32-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application and Claims

Claims 20 and 28-37 are pending. However, only claims 28, 29 and 32-37 are the subject of this Office Action. Claims 20, 30 and 31 are withdrawn from consideration as they belong to a non-elected group of claims. Applicants cancelled claims 2, 15, 17, 19, 21, 23 and 27 in the action filed on 23 September 2010.

Claim 30 and 31 stand withdrawn because the CB1 receptor antagonist to which they are drawn differ from the elected compound. Notably, claims 35-37 are included in the examination currently, because there was no election requirement to specify receptors, only the antagonist.

On 08 September 2008, Applicants responded to a Lack of Unity, which was improperly cast as a "Requirement for Restriction" by the previous examiner on 26 August 2008. The Lack of Unity required the election of a CB1 receptor antagonist and a hepatic disease. Applicants elected N-piperidino-5-(4-chlorophenyl)-4-methylpyrazole-3-carboxamide as the CB1 receptor antagonist and alcoholic liver cirrhosis as the hepatic disease. A search for alcoholic liver cirrhosis did not reveal the existence of applicable prior art and as such, the search was extended. However, Applicants have now amended their claims, canceling claims directed to liver cirrhosis and added new claims, for which hepatic fibrosis is the subject. The latter is the disorder that is the subject of examination herein.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e)

has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicants' arguments filed on 23 September 2010 have been fully considered but are deemed to be persuasive regarding the previous rejection. Rejections not reiterated from this Office's previous action are hereby withdrawn. The rejections set forth herein constitute the complete set of rejections being applied to the instant application presently.

Objections

Objection to the Specification

This application contains sequence disclosures at page 18. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825, because it lacks any submission of a computer readable form sequence listing, a paper copy for the specification, a statement under 37 CFR §§ 1.821(f) and (g), and SEQ ID Nos. cited along with each sequence in the specification or figures. Moreover, there is sequence rule non-compliance, because the sequences on page 18 lack the required SEQ ID NOs.

Applicant is reminded that SEQ ID Nos. are not required in figures, *per se*. However, the corresponding SEQ ID Nos. are required in the Brief Description of the Drawings section in the specification. Applicant is also reminded that a CD-ROM sequence listing submission may replace the paper and computer readable form sequence listing copies.

The paper or compact disc copy of the Sequence Listing is an integral part of the application. If submitted on paper, the Sequence Listing must begin on a new page, should appear at the end of the application, and preferably should be numbered independently of the numbering of the remainder of the application. The new page that begins the "Sequence Listing" should be entitled "Sequence Listing." If not submitted as such at filing, the Sequence Listing must be inserted into the application *via* amendment, *e.g.*, by preliminary amendment. If submitted on compact disc, the specification must contain an incorporation by reference of the material on the compact disc in a separate paragraph, identifying each compact disc.

Applicant is given the same response time regarding this failure to comply as that set forth to respond to this Office Action. Failure to respond to this requirement may result in abandonment of the instant application or a notice of a failure to fully respond to this Office Action.

Objection to the Claims

The disclosure is objected to because of the following informalities: There is a typographical error in instant claim 32, as the dichlorophenyl moiety therein is only preceded by the number "2" and therefore, another number is needed for the other chloro in the dichloro moiety. Appropriate correction is required. However, for the purpose of examination herein, the Examiner presumes the moiety to be 2,4-dichlorophenyl, as noted in the elected compound.

Claim Rejection - 35 U.S.C. §112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 29 is rejected under 35 U.S.C. §112, second paragraph for indefiniteness. The claims fail to particularly point out and distinctly claim the subject matter that the Applicant regards as his invention.

Claim 29, which depends from claim 28, is directed to a method of treating hepatic fibrosis comprising administering a therapeutically effective amount of at least one CB1 receptor antagonist. Claim 29 fails to further limit claim 28 in that claim limitation 29 speaks to a CB1 receptor rather than a CB1 receptor antagonist, and there is no antecedent basis for the same. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28, 29 and 32-37 are rejected under 35 U.S.C. 103(a) as being obvious over Batkai et al. (Nature Medicine, Volume 7, No. 7, 2001, pp.827-832) in view of Caprino, et al, "Alpha- SMA Expression in Hepatic Stellate Cells and Quantitative Analysis of Hepatic Fibrosis in Cirrhosis and In Recurrent Chronic Hepatitis After Liver Transplantation," *Digestive and Liver Disease*, Vol. 37, pages 349-356 (2005)[hereinafter referred to as "Caprino et al"]. The teachings of Batkai et al from this Office's previous actions are incorporated herein by reference entirely.

Notably, claims 35-37 are also properly rejected hereunder, because in assigning the claims their broadest reasonable interpretation, the language "a portion of" is construed as one amino acid and the same is present in all of the sequences and the presence of G-protein coupled receptors understood to be ubiquitous. Insofar as the percentage homology is concerned, it is well understood in the art that the same would be discoverable as an effective percentage using random optimization for the desired/intended effect.

Applicant now argues that the claims no longer read on the prior art of record, because "[h]epatic fibrosis is differentiate from cirrhosis and its treatment is patentably distinct." While the Applicants' argument is appreciated, the same is not met with persuasion given the knowledge that "[hepatic fibrosis, the common final manifestation of several chronic liver diseases, is the result of a prominent accumulation of extracellular matrix (ECM) materials and ultimately can lead to cirrhosis. *Please see* Caprino et al, Abstract at lines 3-4 and 9-20.

Several studies have described that hepatic stellate cells (HSC) play a central role in the pathogenesis of fibrosis." (Caprino, et al, page 349, Col. 2 - page 350, Col. 1, para. 1). So in short, the hepatic fibrosis that is now the subject of the instant invention, pathophysiologically can serve as a precursor to the more serious cirrhosis disclosed by the references of record. *Please see* Caprino et al, Abstract at lines 3-4 and 9-20.

As noted prior, Batkai teaches an administration of CB1 receptor antagonist such as SR141716A (commonly known N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide or rimonabant) to an animal having the advanced cirrhosis associated with the vasodilated state, wherein said SR141716A is administered in 3mg/kg (abstract; page 827, column 2, last paragraph to page 829, column 1, 1st paragraph; Discussion). Batkai teaches that the activation of vascular CB1 receptor, which is the subject of the instant invention, is involved in pathophysiology of liver cirrhosis and the antagonist of CB1 receptor is useful in providing a therapeutic utility in managing patients with advanced liver cirrhosis awaiting liver transplantation.

With respect the instant "from 0.01 mg to 500mg" recited in claim 33, the examiner determines that the referenced 3mg/kg (e.g., average weight of approx. 200g of rat is translated

to approx. 0.6mg) falls within the "metes and bounds" of the instant claimed dosage range. Thus, the reference brings the instant invention within the purview of the prior art.

One of ordinary skill in the art would have been motivated to combine the teachings of Caprino et al with the teachings of Batkai et al to arrive at the instant invention due to the overlap in the scope of the subject matter, most notably both references being directed to cirrhosis, an often long-term effect of hepatic fibrosis.

One having ordinary skill in the art would have also expected, as taught by Batkai et al, that compounds having CB1 receptor antagonist activity would be useful in the treatment of hepatic fibrosis and cirrhosis of the liver, particularly advanced cirrhosis of the liver associated with vasodilated sate (which contributes to portal hypertension and the development of ascites). In view of the foregoing, therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was contemplated to devise a method of treating hepatic fibrosis by administering to a patient in need thereofa CB1 receptor antagonist.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia Hughes whose telephone number is (571) 272-6026. The examiner can normally be reached Monday through Friday from 9:00 am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Alicia R. Hughes/
Examiner, Art Unit 1614

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